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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/720,006	KARL ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-48,73 and 75-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-48,73 and 75-82* is/are rejected.

7)☒ Claim(s) *47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 11/14/2008, is acknowledged and has been entered. Claims 44-45 and 48 were amended. New claims 81-82 have been added. Accordingly, claims 44-48, 73, and 75-82 are currently pending and subject to examination below.

Priority

2. Acknowledgment is made of the present application as a proper National Stage (371) entry of PCT Application No. PCT/EP99/04310, filed 6/22/1999. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Application No. 198 27 714.8, filed on 6/22/1998, and to Application No. 198 38 802.0, filed 8/26/1998, both in Germany.

Objections/ Rejections Withdrawn

3. The objections to claims 44-45, 75, and 77 set forth in the previous Office action have been obviated by Applicant's amendments.

4. The rejections under § 112, 1st paragraph in regards to the calculation of a test area-specific cut-of index (COI) are withdrawn in response to Applicant's arguments that calculation of a COI was well known in the art (Reply, pages 6-8).

5. The rejections under § 112, 2nd paragraph not reiterated below have been withdrawn.

6.

Terminal Disclaimer

7. The terminal disclaimer filed 11/14/2008 is acknowledged but has been disapproved as improper. An attorney or agent, not of record, is not authorized to sign a terminal disclaimer in the capacity as an attorney or agent acting in a representative capacity as provided by 37 CFR 1.34 (a). See 37 CFR 1.321(b) and/or (c).

Claim Objections

8. Claim 47 is objected to because of the following informalities: it appears that the period at the end of the claim has been inadvertently omitted in the current version. Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 44-48, 73, and 75-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

11. Claim 44, as amended instantly, recites a "non-porous support comprising at least two spatially separate test areas **and an inert solid phase**" (step (a), emphasis added). The claim also

recites "calculating a test area-specific cut-off index (COI) on each test area based on a test area-specific background detected from a signal generated by any signal generating group non-specifically bound to the inert solid phase" (see step (d)).

Applicant's Reply states that no new matter has been added and indicates support at page 11 of the specification. The Examiner was unable to find support where indicated.

The term "inert solid phase" could not be found in the specification or claims as originally filed. Page 11 discusses "**control areas**". As best understood, it appears that Applicant believes that the "control areas" provide support for the now-claimed "inert solid phase".

However, although "control areas" are disclosed, the specification does not mention or convey that such areas are inert. The particular nature of the "control areas" is not detailed; for example, it is not discussed what reagents might make up the control areas. Consequently, it cannot be envisaged from the specification that the control areas are "inert".

Inert regions of the solid phase are discussed (page 8, last paragraph), which are differentiated from the test areas. An **inert surface** that exists between the test areas is also mentioned (paragraph bridging pages 12-13). In this context, it is explained that the size of the inert surface (i.e., the distance between the individual test areas) is important so that the test areas do not coalesce.

The specification elsewhere stresses the importance of making sure the test spots are applied in defined areas that do not coalesce (page 4, third full paragraph; page 6, fourth paragraph; page 18, second paragraph).

The invention involves test areas that are spots arrayed on the non-porous support (see, e.g., page 6). Thus the disclosure of inert regions or of an inert surface between the test areas

conveys to the Examiner the regions that surround the test area spots—the regions that have not been printed or arrayed. To use the analogy of a tray of muffins, where the test areas are the muffins themselves and the inert regions/ surface would be the muffin tin itself, designed to prevent the individual muffins from merging or coalescing with each other.

By contrast, Applicant now claims measuring signals from an "inert solid phase". No description could be found of methods in which an inert solid phase is assayed in this manner. No description could be found of methods in which the inert surface between test areas is assayed.

In addition, the claim terminology a "non-porous support comprising at least two spatially separate test areas **and an inert solid phase**" would encompass many things beyond the disclosed "control areas" or the disclosed "inert regions"/ "inert surface" discussed above. This could mean, for example, an additional solid phase layer beneath or above the test areas, such as a housing, a handle, or other type of support. Such embodiments are not disclosed. The specification, in disclosing only inert areas between the test spots or alternatively control areas, fails to convey evidence of possession of all non-porous supports that additionally comprise an "inert solid phase" in addition to test areas.

Furthermore, the term "inert" has not been assigned a specific or limiting definition. In the specification, the term is apparently used to distinguish the spots that have been arrayed on the solid phase from the surrounding regions of the solid phase that have not been printed or arrayed. The latter may be said to be "inert" because they have not been printed with any reagents. Those of ordinary skill in the art would understand that to analyze an array, signals from the arrayed spots that are measured—and not signals from regions in between the spots.

However, the claimed method now involves *measuring signals on the inert areas*. See step (d) in which COI values are calculated "based on **a test area-specific background** detected from a signal generating group **non-specifically bound to the inert solid phase**". Based on the specification, which only discusses "inert" regions or surfaces as those between spots, step (d) as best understood involves measuring signals on the areas between the arrayed spots. Such steps are not clearly disclosed in the specification and would be couterintuitive to those of skill in the art.

Finally, the recitation of a "test area-specific background" that is detected from "signal generating group non-specifically bound to the inert solid phase" might suggest that for each test area, there is a corresponding inert solid phase upon which a measurement is performed (hence "test area-specific"). As discussed above, the specification makes clear that inert regions/ surfaces are distinct from the test areas, e.g., regions in which spotted reagents are not printed or arrayed. As such, it is unclear how signal assessed in the inert area could be considered "**test-area specific** background". The specification does not disclose, for example, using different inert regions/ surfaces that would somehow correspond with each test area.

Similarly, although "control areas" are mentioned, the specification does not provide details regarding the nature of the control areas or indicate that they are "inert". The specification also does not disclose using one control area for each test area. The detailed elements now recited in the claim (background due to signal generating group non-specifically bound) cannot be envisaged from the general disclosure of "control areas".

12. Claim 47 recites that “the solid phase further comprises a control area for detecting false results caused by interferences”. As discussed above, claim 44 has been instantly amended to recite an “inert solid phase” by which interference (background/ non-specific binding) is measured. No description of methods involving a solid phase that comprises both an “inert solid phase” and a “control area” could be found in the specification.

Applicant has indicated support for the instant amendments to claim 44 on page 11 of the specification, which discusses the use of control areas. If Applicant believes that the “control areas” of page 11 are intended to provide support for the element of an "inert solid phase” in claim 44, the dependent claim is repetitive in reciting a “control area”.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 44-48, 73, and 75-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. Claim 44 recites a plurality of analytes "derived from” infection by a pathogen. This terminology renders the claim indefinite because the specification does not define the term "derived from" in this context. Although antigens that are HIV proteins are disclosed, as well as antibodies specific for such proteins, it is unclear what other analytes or types of analytes would also be considered to be "derived from" infection by a pathogen. It is unclear by what process or processes the analytes would be "derived". For these reasons, the metes and bounds of the claim are unclear. Would this encompass, for example, antigens from different viruses that evolved

from a common precursor by mutation in an infected host? Analytes generated through recombinant engineering of known bacterial proteins whose sequences are altered via mutagenesis or other means? Human proteins that are upregulated in response to infection by the pathogen?

15. Claim 44 recites step (d) of calculating a test area-specific COI "based on a **test area-specific background** detected from a signal generated by any signal generating group non-specifically bound to the inert solid phase". It is unclear what is meant by a "test area-specific" background. In what sense is the background measurement specific for a particular test area? The claim appears to imply that each different test area would have a corresponding background measurement. However, the claim only recites one "inert solid phase". It is therefore unclear in what sense the signal generated on the inert solid phase may be said to be "test area-specific", or for which of the two test areas the background signal is specific for.

16. Claim 47 recites the limitation "the solid phase". There is insufficient antecedent basis for this limitation in the claim. Claim 44 now recites both a "solid phase" and an "inert solid phase", such that there is ambiguity as to which solid phase is intended for claim 47.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

18. Claims 44-45, 47-48, 73, 76-79, and 81 are rejected under 35 U.S.C. 102(a) as being anticipated by Karl et al. (WO 99/05525, Applicant's Information Disclosure Statement of 6/15/07).

It is noted that while the reference is a German language document, an English translation is available by way of its U.S. counterpart, US 6,815,217 B2 (of record). The column and line numbers indicated below refer to the text of US 6,815,217 B2.

Karl et al. teach a method for detecting at least one analyte in a sample using a solid phase having at least one spatially discrete test area and at least one control area used to detect nonspecific binding. See the abstract and column 1, line 66 to column 2, line 61; column 6, lines 56-64; and claim 17 in particular. The solid phase is preferably non-porous, e.g. plastic, glass, metal, or metal oxide (column 2, lines 29-32). In one embodiment, a plurality of analytes derived from a single pathogen are assayed, namely HBs antigen and anti-HBc antibodies (which would be considered to be each "derived from" hepatitis B virus). Immobilized antibody specific for HBs antigen (i.e., first receptor) and immobilized HBc antigen (i.e., second receptor) are bound to discrete test areas on the solid support. See Figure 1 and column 2, lines 3-20, 34-39, and line 62 to column 3, line 14.

The control areas of Karl et al. would be considered to represent an "inert solid phase" in the absence of a specific or limiting definition for this term, in that the control areas detect non-analyte interfering components that bind nonspecifically to the solid phase (column 2, lines 1-3 and 17-20; column 3, line 59 to column 4, line 60). For example, the control areas can contain non-analyte specific antibodies, which would be considered "inert" areas in that they do not react with analyte.

The reference further teaches contacting the sample with the solid support and with a detection reagent, namely a specific binding reagent for the analyte having a suitable marker group, e.g. fluorescent marker group, and the detection reagent may be a "universal" marker group. See column 2, lines 39-64; column 3, line 17; claim 34, step (b) and Figure 1. The signals from the marker groups are separately measured for each test area (see column 6, lines 34-45 and the Tables presented in the Examples). This is also made clear for example in claim 19, where test and control areas are separately measured in steps (c) and (d), respectively.

Karl et al. further teach calculating a test area-specific cut-off index (COI). See column 5, line 66 to column 6, line 45, and in particular in the Tables presented in the examples. For the case of the analyte HBs antigen, Karl et al. teach that a COI greater than 1 indicates a positive test, i.e. the presence of the analyte (see column 8, lines 1-24). Karl et al. discuss how the calculations are based on measured values in the control; these measured values are due to interference or unspecific binding (i.e., presence of the signal generating group non-specifically bound to the inert solid phase). See column 2, lines 1-3; column 3, line 34 to column 4, line 60; column 5, line 66 to column 7, line 4. As discussed above, the control areas may have solid phase receptors that contain an unspecific antibody or alternatively may not contain any solid phase receptor (see column 4, lines 5-48; and Example 1, see legend to the table).

With respect to claim 47, Karl et al. teach control areas for detecting false results caused by interferences (see, e.g., the abstract; column 1, lines 11-33; column 2, lines 21-28; column 3, line 30 to column 4, line 60; and column 10, lines 45-49).

With respect to claim 48, Karl et al. teach universal marker groups comprising fluorescent latex beads (column 2, lines 62-67 and Figure 1).

With respect to claims 78-79, Karl et al. teach calculating the COI by the formula COI = [Signal (test field) – signal (negative control field)]/3 x signal (negative control). See the Tables in the Examples, e.g. at column 8, lines 19-20. Absent a specific or limiting definition for the variables recited instantly, this equation reads on that currently recited even though slightly different terminology is used. Specifically, the "Signal (test field)" of Karl et al. denotes the signal measured in the test, i.e. sample area. Karl et al. indicate that the negative control field refers to unspecific binding in the control field without solid phase receptor (column 8, lines 17-18), such that "signal(negative control field)" would read on the instantly claimed "$background_{sample}$" since it denotes signal due to the nonspecific interaction of sample with the solid support, i.e. background. The value 3 would be considered "n" and the signal (negative control) would read on the instantly recited "$background_{negative\ control}$" since signal associated with a negative control would be considered "background" signal since it is not reflective of the presence of analyte.

With respect to claim 81, Karl et al. teach detection of the hepatitis B antigen HBsAg and of antibodies to same (Figure 1).

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claim 46 is rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Karl et al.

Karl et al. is as discussed above, which teaches that the test areas most preferably have a diameter of 10 microns (0.01 mm) to 2 mm (column 2, lines 9-10). Such a range largely overlaps the claimed range of 0.01 mm to 1 mm, such that the claimed range is anticipated with sufficient specificity in the absence of evidence of criticality for the narrower range. See MPEP 2131.03.

However, even if the range of 0.01 mm to 1 mm is held not to be anticipated with sufficient specificity by the prior art range of 0.01 mm to 2 mm, a *prima facie* case of obviousness also exists given that the claimed range largely overlaps the prior art range. See MPEP 2144.05. As such, it would have been obvious to one of ordinary skill in the art to arrive at the claimed range by selecting values within the prior art range out of the course of routine optimization. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

21. Claim 80 is rejected under 35 U.S.C. 103(a) as being unpatentable over Karl et al. in view of Ohkawa et al. ("Hepatitis C virus antibody and hepatitis C virus replication in chronic hepatitis B patients" J Hepatol. 1994 Oct;21(4):509-14), Ohnishi et al. ("Detection of anti-hepatitis C virus antibody in fulminant hepatic failure" Gastroenterol Jpn. 1991 Jul;26 Suppl 3:212-5), Hyman et al. (US 5,384,240), Chan et al. (US 5,120,662, of record), Lesniewski et al. (US 6,596,476 B1), Kiyosawa et al. ("Significance of IgM antibody to hepatitis B core antigen for the differential diagnosis of acute and chronic hepatitis B virus infection and for the

evaluation of the inflammatory activity of type B chronic liver diseases" Gastroenterol Jpn. 1986 Dec;21(6):601-7), and Yuki et al. ("The significance of immunoglobulin M antibody response to hepatitis C virus core protein in patients with chronic hepatitis C" Hepatology. 1995 Aug;22(2):402-6).

Karl et al. is as discussed above, which teaches the equation COI = [Signal (test field) – signal (negative control field)]/**3** x signal (negative control), where 3 corresponds to the instantly claimed "n". However, the reference fails to specifically teach using a value of 2 instead of a value of 3 in the above equation.

However, when taken together with the general knowledge in the art of clinical diagnostics, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention by optimizing the equations disclosed in Karl et al. The following references are cited as relevant in establishing the general knowledge available in the prior art.

Ohkawa et al. teach calculating the ratio of sample values to the cut-off value to give a "cut-off index" that allows for assay results to be compared when assaying for hepatitis C virus antibody. See especially page 510, left column, last full paragraph and page 511, right column and Figure 1.

Ohnishi et al. similarly teach that in an assay for anti-HCV antibodies, levels were deemed positive when the cut-off index was greater than 1, the cut-off index being the ratio of the signal of the sample to that of a cut-off value (page 213, left column).

Hyman et al. teaches determining the signal-to-cut-off ratio (S/CO) in a method for screening for the presence of HIV-1 p24 antigen, in which values of this ratio that are greater than 1 are considered positive (Example 1, see especially at column 6, lines 5-9).

Chan et al. teach determining sample to cutoff values (S/CO) in an HCV assay, where S/CO values greater than or equal to 1.0 were considered reactive (Example 15, columns 15-16).

Yuki et al. teaches assessing samples as positive when they have a cut-off index > 1, where the cut-off value is taken as 4 times the mean negative control sample signal (abstract and page 403, left column, last paragraph).

These teachings indicate that it was routine in the art to calculate cut-off indices (also known as signal-to-cutoff ratios), where the signal from a sample is divided by a cutoff value, for the purpose of assessing whether the sample is positive or negative. Moreover, the reference teachings establish that it was known to assess whether a sample was positive when the value of the cut-off index or signal-to-cutoff ratio was greater than 1.

The prior art also recognized that cutoff values (i.e., the denominator by which the signal is divided) may be established using data from negative control samples.

For example, Lesniewski et al. discuss how cutoff levels should be selected in order to maintain acceptable assay specificity (column 12, lines 51-58). Such cutoff values should clearly separate most of the presumed "true negatives" from "true positive" specimens. The reference teaches that a general cutoff value may be calculated as about 2.1 to 8 times the negative control mean absorbance value (ibid and column 18, lines 49-56).

Kiyosawa et al. assayed for antibodies to HBc and expressed their results using the equation:

cut-off index = (net count of sample / mean of net count of negative control) x 1 / 2.1

See page 603, left column.

Yuki et al. teaches assessing samples as positive when they have a cut-off index > 1, where the cut-off value is taken as 4 times the mean negative control sample signal (abstract and page 403, left column, last paragraph).

When taken together, these various references serve to indicate that it was well known in the art of clinical diagnostics to relate assay signals to a cutoff or threshold value in order to assess the results of the assay, i.e. to decide whether a sample is positive or negative. One way in which this was often done in the prior art was to divide the assay signal by a cut-off value, known as calculating the signal-to-cutoff ratio or "cut-off index". It was further known to establish such a cutoff value by reference to a negative control. More particularly, it was known to establish cutoff values by multiplying the negative control signal by various numerical values.

As such, one of ordinary skill in the art would recognize that the equation for calculating a cutoff index (COI) in Karl et al. represented a variation on such known cutoff index calculations, where the cutoff level in Karl et al. is being obtained by multiplying the negative control signal by a value of 3.

Because the value of the selected cutoff was known to affect how the results of the assay are interpreted, i.e. whether a given sample would be classified as positive or negative, it is apparent that the cutoff value was recognized in the prior art to be a result-effective variable.

Although Karl et al. exemplify multiplying the negative control signal by 3 for those analytes such as HBsAg that were studied in the Examples, the reference clearly contemplates detection of analytes in general.

As such, absent evidence of criticality it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention out of the course of routine optimization of the cutoff

value, which was known to involve multiplying the negative control signal by a numerical variable. One would be motivated to do this in order to optimize an assay for a given analyte to ensure that samples were more likely to be correctly classified as positive or negative. For example, when using the method of Karl et al. to detect other analytes for which data is not presented in the Examples of Karl et al., it would have been obvious to apply a known technique for obtaining appropriate cutoff values, namely that of multiplying the signal for a negative control sample by a numerical variable, to the known method of detecting a plurality of analytes of Karl et al.

22. Claims 44-45, 47-48, 73, and 75-77, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor (US 5,627,026).

O'Connor et al. teach a method of detecting a plurality of analytes, namely both an antibody to and an antigen of infective agents in a single sample aliquot. See the title, abstract; and column 1, line 58 to column 4, line 41.

O'Connor et al. teach that the infective agent may be FeLV, FIV, or HIV (column 4, lines 14-30) and assessment of simultaneous assay for antigens and antibodies associated with the same viral infection (i.e. derived from one pathogen), is clearly disclosed at lines 23-25.

The method of O'Connor et al. involves (a) providing a solid phase (solid support), which may be a non-porous material such as a microtiter well, or a glass, plastic, or latex bead (see especially column 3, lines 17-29; column 4, line 65; column 6, line 57 to column 8, line 3). An antigen capable of selectively forming an immune complex with a sample antibody (i.e., first analyte-specific receptor) is bound to the solid support at a first location, and an antibody capable

of selectively forming an immune complex with a sample antigen (i.e., second analyte-specific receptor) is bound to the solid support at a separate position (see column 2, line 4 to column 3, line 7; and especially claims 1, 7, 9, and 14).

The solid support may additionally contain positive and negative control spots (column 3, lines 26-29; column 5, line 48 to column 6, line 6; and column 8, lines 59-65). Negative controls can be coated with non-specific mouse antibody and purified uninfected host cell antigen sufficient to mimic "nonspecific" reactions (column 5, lines 48-63). Consequently, the negative control spots may be considered an "inert solid phase" as they do not specifically bind to analyte. The negative controls are exposed to all assay reagents in a fashion identical to the sample spots (ibid and column 8, line 30 to column 9, line 24). Thus, it is implicit that the signal due to bound signal generating group in the negative control areas is also measured the same as for the test areas. Such a measurement of the negative control areas reads on the instantly claimed "test area-specific background detected from a signal generated by any signal generating group non-specifically bound to the inert solid phase".

O'Connor et al. further teaches (b) contacting the sample with the solid phase and with detectable reagents. See column 3, lines 8-51, and claim 1 in particular. For example, O'Connor et al. discloses the use of a labeled antigen (i.e., third receptor) that selectively binds to a captured antibody from the sample, together with the use of a labeled antibody (i.e., another third receptor) that selectively binds to a captured antigen in the sample in a method for detecting both antibody and antigen in a single sample (claim 1). The signals generated by the detectable labels are (c) separately measured or assessed (column 5, lines 43-47 and line 65 to column 6, line 6; and the claims, e.g. claim 1, step (e)).

Regarding the step of calculating a test area-specific cut-off index, O'Connor et al. teaches measuring the signal from the signal generating group (e.g., the absorbance value at 650 nm due action of the enzyme label on TMB colorimetric substrate) for both samples and controls (positive and negative controls). This is done in order to determine whether the assay is valid: anything 3 times greater in absorbance intensity than the negative control is regarded as positive. See column 8, line 30 to column 9, line 25, and in particular at column 9, lines 17-25.

This value, the ratio of the signal from the sample well to that of the signal due to a well with negative control serum, would be considered a "test area-specific cut-off index (COI)" in the absence of a specific or limiting definition for this term. The COI taught by O'Connor et al. is 3, which is larger than 1 and therefore reads on the limitation "wherein a COI larger than 1...is indicative...".

In addition, the calculation of the COI by O'Connor involved measurement of signals from negative controls, in which antigen-coated wells were contacted with samples known not to contain analyte (column 8, lines 59-62). Labeled third receptor was added (e.g., HRPO conjugate as in column 9) and then the label from the signal measured. In the case of the negative control wells, any bound label measured would be attributable to nonspecific binding since no analyte was present. Furthermore, the reference makes clear that the absorbance intensity of each well was compared to the negative control. Consequently, this comparison would be considered "test area-specific" as it involved each test area signal.

Likewise, in the embodiments involving a filter as the solid support, the reference makes clear that each *respective* sample spot is assessed in relation to the control spot in order to determine whether the assay results are positive. See column 5, line 48 to column 6, line 6.

The O'Connor et al. reference differs from the claimed invention in that the discussion of relating the A_{650} value of the sample to the negative control value is only discussed for the FIV antibody ELISA test, which only involved this one analyte and not a plurality of analytes.

However, given that O'Connor et al. focus on the determination of both antibody and antigen in a sample, it would have been obvious to one of ordinary skill to also relate the signal value of the sample for antigen test areas as well. In particular, when detecting both antigen and antibody as taught by O'Connor et al., it would have been a matter of routine skill in the art to construct positive and negative controls for both antigen and antibody analytes to be detected. For example, when detecting FIV antigen in addition to FIV antibody, it would have been obvious to include a negative control for FIV antigen and to relate the signal from an FIV antibody-coated well to the signal from the negative control, thereby measuring background due to non-specific binding.

Furthermore, it would have been obvious to apply the known technique for analyzing the results from each reaction (e.g., from each sample well) in the same manner as described for the FIV antibody. One would be motivated in light of the clear teaching of O'Connor et al. that this relation of sample signal to control signal allows for the validity of the assay to be determined. As such, it would have been obvious to calculate a COI for antibody as well as for antigen in order to determine whether the sample was in fact positive for the presence of each of these analytes.

With respect to claim 45, O'Connor et al. teach detection of both HIV antigen and anti-HIV antibody (column 4, lines 23-25). Hepatitis B (i.e., HBV) antigen is also contemplated (see column 4, lines 6 and 17 and claim 13).

With respect to claim 47, O'Connor et al. teach controls, e.g. control wells coated with receptor and to which positive or negative control sample is added (column 8, lines 59-65). Alternatively, a negative control can be performed with a non-specific antibody (column 5, lines 48-65). This is done to control for nonspecific reactions, i.e. "interferences".

With respect to claim 48, O'Connor et al. teaches detection reagents comprising a third receptor specific for the analyte (e.g., antibody or antigen specific for antigen or antibody, respectively) bound directly to a signal-generating group (enzyme). See column 3, lines 8-51; column 7, lines 8-30 and 47-51; column 8, lines 50-56).

With respect to claim 76, O'Connor et al. teaches that the detectable labels may be enzyme labels (column 3, lines 47-51).

With respect to claim 75, O'Connor et al. teaches detecting HIV p24 antigen and anti-HIV antibody (column 4, lines 23-30).

With respect to claims 77 and 81, O'Connor et al. teaches detection of Hepatitis B (i.e., HBV) antigen (see column 4, line 6) but fails to specifically teach detection of more than one analyte "derived from" HBV. Nonetheless, O'Connor et al. teach simultaneous assaying for antigens and antibodies associated with the same viral infection (column 4, lines 23-25). Although HIV and not HBV is exemplified in this context, it would have been obvious to one of ordinary skill in the art to select HBV from the finite number of viruses disclosed in the reference and to detect both HBV antigen in addition to anti-HBV antibody.

23. Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor et al. in view of Ekins (US 5,837,551, of record).

O'Connor et al. is as discussed above, which teaches test areas on non-porous solid supports such as microtiter plates. However, the reference fails to specifically teach that the test areas have diameters of 0.01 – 1 mm.

Ekins teaches forming arrays of "microspots" in which binding agents (i.e., receptors) are immobilized into defined, spatially separated test zones (i.e., "test areas") on a solid support (column 2 line 35 to column 4 line 41). The microspots preferably have an area of less than 1000 square microns, e.g. 0.1 square mm, and can be for example of diameter 80 microns or 0.08 mm (column 3, lines 34-63; column 4, line 2). By providing such microspot arrays, a plurality of analytes may be simultaneously determined (column 3, lines 40-47). The microspots can be formed on a microtiter plate, i.e. non-porous support (column 7, lines 33-40). Binding of analytes to the binding agents immobilized in each microspot is then assessed using a detection agent capable of binding to the analyte and including a marker, e.g. an enzyme or fluorescent marker (column 3, lines 10-33).

Such miniaturized test zones contain small amounts of binding agent, allowing binding assays to be conducted with rapid kinetics to minimize the time needed to complete the assay (column 6, lines 4-8). In addition, less of the binding agent is necessary, diffusional constraints are reduced and assay sensitivity is also improved (column 6, lines 9-32).

Therefore, it would have been obvious to one of ordinary skill in the art to modify the method of O'Connor et al. by depositing the first and second receptors into small test zones or "microspots" (e.g., of diameter 0.08 mm on a microtiter plate) as taught by Ekins et al. because detection of antibody and antigen could be conducted more rapidly and with greater sensitivity and would also require less of the capture reagents to be consumed.

When performing the method of O'Connor et al. using microspots in this manner, it would have been further obvious to employ the detection scheme taught by Ekins to be suitable for the microspot arrays, namely by using a detection agent capable of binding to analyte (i.e., third receptor) and including a marker capable of producing the signal for the assay.

24. Claims 78-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor in view of Betts Carpenter ("Enzyme-Linked Immunoassays" In: Manual of Clinical Laboratory Immunology, Noel R. Rose et al. (Eds), ASM Press, Washington, DC (1997) Fifth Edition, pages 20-29, Ohkawa et al., Ohnishi et al., Hyman et al., Chan et al., Lesniewski et al., Kiyosawa et al., and Yuki et al.

O'Connor et al. is as discussed above, which teaches a method substantially as claimed in which a cut-off index is calculated by relating the sample signal to the signal from a negative control. In particular, O'Connor et al. teach that an absorbance signal greater than 3 times the mean negative control absorbance indicates that the sample is positive (column 9, lines 17-25).

However, O'Connor et al. differs from the claimed invention in that it fails to specifically teach first subtracting "background $_{\text{sample}}$" from the numerator in the above equation. The reference also fails to specifically teach multiplying "background $_{\text{negative control}}$" by a number n between 2 and 100, or in particular between 2 and 10, or in particular by 2.

Regarding subtraction of "background $_{\text{sample}}$", it was known in the art to subtract background measurements in order to obtain a net signal. For example, Betts Carpenter teaches that when detecting colorimetric substrates by spectrophotometry in ELISA assays, OD measurements (i.e., the assay signals) can be blanked on air, or alternatively on a well containing

either substrate, substrate-Ab conjugate alone, or a negative serum in an uncoated well (see especially page 25, "Substrates").

Therefore, although O'Connor et al. is silent as to whether the absorbance signal taken represented a signal from which background was subtracted, it would have been obvious to subtract background from the raw absorbance signal in accordance with routine laboratory procedures. For example, it would have been obvious to blank the spectrophotometer on air or on a well containing colorimetric substrate in the method of O'Connor et al., which would be tantamount to subtracting a background measurement for the sample to produce a corrected signal. Blanking a spectrophotometer, as taught by Betts Carpenter, would be at once envisaged by a person of ordinary skill in the art familiar with such equipment. One would be motivated to combine the reference teachings in this manner because Betts Carpenter relates to laboratory procedures for performing ELISA assays, which is the method used in O'Connor et al. as discussed above.

Regarding the multiplier *n* in the denominator of the equation recited in claim 78, O'Connor et al. analyzed the results of the FIV antibody assay by assessing whether the signal-to-negative control ratio was greater than 3. It would also be a simple matter to determine this by simply multiplying the negative control absorbance by 3, and then determining whether the signal value was greater than this value, i.e. whether $\text{Signal}_{\text{sample}}$/ $\text{background}_{\text{negative control}}$ is greater than 1. In such a case, the value 3 as taught by O'Connor would be equivalent to the instantly claimed *n*. As such, it would also have been obvious to arrive at the claimed invention of claims 78-79 by relying on simple algebraic calculations in the course of assessing whether the signal-to-negative control ratio was greater than 3 as directed by O'Connor et al.

This feature of dividing by a multiplier of the negative control value is also found obvious in view of the teachings of Ohkawa et al., Ohnishi et al., Hyman et al., Chan et al., Lesniewski et al., Kiyosawa et al., and Yuki et al. As discussed in detail above, these references establish that it was known in the art to calculate signal to cutoff ratios (also known as "cut-off indices"), and further that the value of the cutoff may be selected based on data obtained from a negative control.

When taken together, these various references serve to indicate that it was well known in the art of clinical diagnostics to relate signals from an assay to signals that of a cutoff or threshold value in order to assess the results of the assay, i.e. to whether a sample is positive or negative. One way in which this was often done in the prior art was to divide the assay signal by a cut-off value, known as calculating the signal-to-cutoff ratio or "cut-off index". It was further known to establish a cutoff value using a negative control. Specifically, it was known to establish cutoff values by multiplying the negative control signal by various numerical values, or alternatively by adding various numerical values to the negative control signal.

Furthermore, as discussed above the value of the selected cutoff was known to be a result-effective variable that affects how the results of the assay are interpreted, i.e. whether a given sample would be classified as positive or negative.

As such, absent evidence of criticality it would have been obvious to one of ordinary skill in the art to modify the teachings of O'Connor et al. and Betts Carpenter, in which a blanked signal is divided simply by the straight, unadjusted negative control absorbance, by first multiplying the negative control signal by a numerical value prior to determining the signal-to-control ratio cut-off index). In particular, in light of the general knowledge in the prior art (as

taught by Ohkawa et al., Ohnishi et al., Hyman et al., Chan et al., Lesniewski et al., Kiyosawa et al., and Yuki et al.), it would have been obvious to optimize the value of the parameter to which the signal from the sample is compared in this manner out of the course of routine optimization in order to ensure that samples were more likely to be correctly classified as positive or negative. For example, when using the method of O'Connor et al. and Betts Carpenter to detect other analytes besides the exemplified FIV antibody, it would have been obvious to apply a known technique for obtaining appropriate cutoff values, namely that of multiplying the signal for a negative control sample by a numerical value, and then dividing the signal by this product, to the known method of detecting a plurality of analytes of O'Connor et al. in order to optimize the assay. It would have been further obvious to arrive at the claimed value of n (e.g., n=2) out of the course of routine optimization, given that the cut-off value (a component of which is n) was recognized in the art as a result-effective variable.

25. Claim 82 is rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor in view of Miyamura et al. (U.S. 5,714,314), or in the alternative as being unpatentable over Karl et al. in view of O'Connor et al., and Miyamura et al.

Karl et al. and O'Connor et al. are as discussed in detail above. Karl et al. teaches assaying for HBV antibodies and antigens using immobilized HBs antigen and anti-HBs antibody, respectively (see especially Figure 1). However, the reference fails to specifically teach assaying for HCV antigens and antibodies.

O'Connor et al. teaches simultaneous assay for antigens and antibodies associated with the same viral infection, e.g. HIV antigen and anti-HIV antibody, in order to rapidly screen blood

or other biological fluids for infective agents such as HIV (see column 4, lines 14-30). The references also mentions hepatitis in general, teaching how hepatitis antigen and anti-hepatitis antibody can be immobilized onto the solid support (to thereby detect hepatitis antibody and antigen, respectively). See column 2, lines 40-59 and column 3, lines 17-29). However, the reference fails to specifically teach detection of hepatitis C.

Miyamura et al. teaches that HCV was known in the art to be one type of pathogenic virus causing viral hepatitis. The reference further teaches that HCV was known as a grave infectious disease worldwide, and the prevention, early diagnosis, and treatment thereof were of recognized importance. See column 1, lines 30-44. Miyamura et al. also discuss how hepatitis C antigen can be used to detect antibody to HCV, e.g. in blood samples (abstract).

Therefore, it would have been obvious to one of ordinary skill in the art to select HCV as taught by Miyamura et al. as the type of viral infection in the method for simultaneous assay for antigens and antibodies associated with the same viral infection of O'Connor et al. More particularly, it would have been obvious to employ anti-HCV antibody and HCV antigen as first and second receptors to detect HCV antigen and anti-HCV antibody, respectively, as the plurality of analytes. One would be motivated to do this because HCV was recognized as a disease of significant clinical concern, as taught by Miyamura et al. Motivation to combine the references also comes from the teachings of O'Connor et al., who teach detection of hepatitis in general albeit not the subtype of HCV. One would have had a reasonable expectation of success because anti-HCV antibodies and HCV antigens were known in the art (as taught by Miyamura et al.).

Similarly, although Karl et al. exemplify detection of HBV antibodies and antigens, it would have been obvious to one of ordinary skill in the art to detect HCV antigens and antibodies in light of the teachings of Miyamura et al. that HCV was of significant clinical concern. Moreover, in light of the teachings of O'Connor et al. that simultaneous assays that screen for both antigens and antibodies in a single test provides a means for rapid screening for infective agents, one would be motivated to detect HCV antibodies and antigens simultaneously a single test in order to rapidly screen for the presence of HCV.

Double Patenting

26. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

27. Claims 44-48, 73, and 75-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 6,815,217 in view of Schonbrunner (GB 2 313 666 A, of record).

U.S. Patent No. 6,815,217 claims an assay device and method for determining an analyte, in which a solid phase is provided that contains a receptor that includes a binding site for specifically binding with the analyte (i.e., analyte-specific receptor) in a defined region of the support (see especially claim 19). The analyte may be HIV antibodies, HBs antigens, and HBc antibodies (claims 18 and 30). The solid phase may also include a control area that includes an altered receptor incapable of specific binding to the analyte (i.e., "inert solid phase"; see claims 5 and 19). The solid phase may be provided together with a third receptor capable of binding to the analyte, which receptor may include a signal generating group (see claims 19 and 34).

U.S. Patent No. 6,815,217 further recites that the amount of analyte can be quantitatively determined by correcting the value of the signal generated by the marker in the test area to the signal generated by the marker in a control area (claims 19-22). This may involve subtraction of these values (claim 22), i.e. a calculation. In the absence of a specific or limiting definition of the term "cut-off index", the value obtained by this calculation may be considered such an index.

Although US 6,815,217 fails to specifically recite that a COI larger than 1 indicates the presence of a specific analyte, when the claims are given their broadest reasonable interpretation such a statement may be interpreted as merely a characterization or conclusion of the method steps earlier recited. For example, such a statement could be reasonably interpreted as simply reflecting fundamental physiological relationships of the analytes that are determined, which would necessarily apply in the assay method. The recited "wherein" phrase does not clearly call for an active method steps to be performed or designate structural limitations. For all of these reasons, the calculation performed in US 6,815,217 reads on that claimed instantly.

Regarding the claimed "plurality of analytes" that are detected, US 6,815,217 does recite that the solid support may also comprise a second test area in a separate defined region that comprises a second receptor that is specific for a second analyte (see claim 17 in particular). However, US 6,815,217 differs from the instant claims because there is no explicit recitation that the method detects both the first and second analyte, i.e., a "plurality of analytes derived from one pathogen". In addition, US 6,815,217 does not specifically recite that the support is "non-porous".

However, it would have been obvious to one of ordinary skill in the art to envisage that a solid support containing first and second receptors specific for first and second analytes was intended for the purpose of detecting both first and second analytes. Furthermore, the analytes detected in US 6,815,217 may be for example antibodies or antigens, in particular HIV antibodies or HBs (hepatitis B) antigens or HBc antibodies (see claims 18 and 30).

As such, it would have been obvious to one of ordinary skill in the art to perform the method of US 6,815,217 using a solid support having receptors for both HBs antigens and HBc antibodies as the analytes, given that these two analytes are clearly recited as part of a finite list of preferred analytes to be detected. One would be motivated to arrive at such a combination and would have a reasonable expectation of success in so doing since US 6,815,217 recites a device comprising multiple test areas containing multiple receptors for specifically binding to multiple analytes. The use of such a multiply-coated device for the purpose of detecting multiple analytes would be at once envisaged by the person of ordinary skill in the art.

In addition, Schonbrunner et al. teaches that the detection of both HIV antigen and antibody in a sample allows HIV to be specifically detected at a very early stage of the infection

(pages 2-3 and 6-7). Schonbrunner et al. also teaches that antigens or antibodies can be attached to a support in order to detect HIV antibody and antigen, respectively (page 20). The solid support is not critical and can be any material which is insoluble or can be made insoluble, e.g. glass, plastic, metal, or a microtiter well (page 20, lines 9-14).

Therefore, it would also have been obvious to one of ordinary skill in the art to employ first and second receptors for HIV antigen and antibody, respectively, in the method of U.S. 6,815,217 B2 in order to detect HIV infection earlier in light of the teachings of Schonbrunner. In particular, would be modify the teachings of US 6,815,217, in which HIV antibody alone may be detected as the analyte, by detecting both HIV antibody and HIV antigen so as to allow for HIV infection to be detected and in particular at an early stage of infection.

It is noted that the method and device of U.S. 6,815,217 B2 employs separate test and control areas that are separately measured for signal (see especially steps (c) and (d) of claim 19). Therefore, when performing the method of U.S. 6,815,217 B2 and Schonbrunner et al. to detect HIV antibody and antigen, it would have been further obvious to employ this known technique in order separately detect signals in the test areas for each of these two analytes in the same manner. Likewise, it would have been obvious to calculate subtract the signal from the control area from the signal for each analyte (i.e., calculate a test area-specific COI for each test area) when detecting a plurality of analytes according to the method of U.S. 6,815,217 B2 and Schonbrunner et al. so that the amount of each analyte could be quantitatively determined in the same manner as for a single analyte.

Furthermore, although US 6,815,217 does not specifically recite that the solid phase comprises a “non-porous” support, it would have been obvious to one skilled in the art to employ

the specification as a dictionary in order to interpret the meaning of the term "solid phase support" in carrying out the claimed invention. In introducing the solid phase support, the specification of US 6,815,217 at column 2, lines 29-32 states that the support is preferably non-porous. In addition, in light of the teachings of Schonbrunner et al. which indicate that the material for a solid support on which capture reagents are attached can be such non-porous supports as plastic or glass, it would have been further obvious to one of ordinary skill in the art to select such a known material for its known purpose with a reasonable expectation of success.

With respect to claim 46, US 6,815,217 recites that the solid support test area and control area may each have a diameter of 10 microns - 1 cm (claim 14), i.e. 0.01 mm - 10 mm. Because the claimed range of 0.01 - 1 mm lies inside the range recited in US 6,815,217, a prima facie case of obviousness exists (see MPEP 2144.05). Therefore, it would have been obvious to one of ordinary skill in the art to arrive at the claimed range in the course of routine optimization, out of the normal desire of artisans to improve on what is already known.

With respect to claim 47, US 6,815,217 recites that the solid support may include a control area for binding to interfering substances (claims 19 and 34, steps (a)(ii) and also claims 1-8 and 27-28).

With respect to claim 48, US 6,815,217 recites a marker that is capable of generating a detectable signal and binding with the analyte (i.e., third receptor). See claim 34 of US 6,815,217.

With respect to claim 75, US 6,815,217 recites HIV antigens as possible analytes but does not specify specific HIV antigens and antibodies. Schonbrunner et al. further teaches that simultaneous detection of the presence of both antigen and antibody analytes of HIV in a sample

provides a possibility for specifically detecting the presence of HIV in a sample at a very early stage of infection. See pages 5-6, especially at the paragraph bridging the pages and at page 6, lines 26-29. The HIV-1 antigen p24 is taught, although other HIV gag antigens are contemplated (page 6, lines 29-32 and page 25). Detection of antibodies to HIV gp41 is also taught (page 26, lines 4-9).

Therefore, it would have been further obvious to one of ordinary skill in the art to employ the method of US 6,815,217 in order to detect both HIV antigen (e.g., p24) in addition to the anti-HIV antibodies recited in US 6,815,217 because this would allow for HIV to be detected at an earlier stage of infection, thereby closing the diagnostic window. It would have been further obvious to detect those anti-HIV antibodies that target HIV gp41 as taught by Schonbrunner

With respect to claim 76, US 6,815,217 recites a marker capable of generating a detectable signal but does not specifically recite those types of markers recited. Schonbrunner teaches markers or labels that are used to generate a measurable signal (page 23, lines 4-34). In particular, Schonbrunner et al. teach chemiluminescent compounds, enzymes, fluorescent compounds and others. Therefore, it would have been further obvious to employ a chemiluminescent group or an enzyme as taught by Schonbrunner as the marker in the method of US 6,815,217 since these were known to be suitable for the purpose of generating a measurable signal, which is the same purpose for which the markers in US 6,815,217 are employed.

With respect to claim 77, US 6,815,217 recites detection of HIV antibodies but does not specify the type of HIV. Schonbrunner teaches that HIV-1, HIV-2, and HIV-3 variants were known, and that the detection of a variety of HIV's can be achieved by using the appropriate capture reagents (pages 8-9, 15, and 33). Given that a finite number of types of HIV were known

in the art as indicated by Schonbrunner, it would have been obvious to detect analytes "derived from" HIV-1, HIV-2, and/or HIV-3 because these were the types of HIV known in the art. Therefore, one would be motivated to detect analytes associated with any of these known strains in order to assess HIV infection.

28. Claims 78-80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 6,815,217 in view of Schonbrunner (GB 2 313 666 A) as applied to claim 44 above, and further in view of Ohkawa et al., Ohnishi et al., Hyman et al., Chan et al., Lesniewski et al., Kiyosawa et al., and Yuki et al.

U.S. Patent No. 6,815,217 is as discussed above, which recites subtracting signal from a control area from signal in the test area, i.e. "$Signal_{sample}$" - "$background_{sample}$" (see especially claims 19 and 22). However, U.S. Patent No. 6,815,217 fails to specifically recite dividing the resulting value by n x $background_{negative\ control}$, where n is between 2 and 100, between 2 and 10, or is 2.

The teachings of Ohkawa et al., Ohnishi et al., Hyman et al., Chan et al., Lesniewski et al., Kiyosawa et al., and Yuki et al. are discussed in detail above. When taken together, these various references serve to indicate that it was well known in the art of clinical diagnostics to relate signals from an assay to cutoff or threshold values in order to assess the results of the assay, i.e. to conclude whether a sample is positive or negative. One way in which this was often done in the prior art was to divide the assay signal by a cut-off value, known as calculating the signal-to-cutoff ratio or "cut-off index". It was further known to establish a cutoff value using a negative control. Specifically, it was known to establish cutoff values by multiplying the

negative control signal by various numerical values, or alternatively by adding various numerical values to the negative control signal.

Furthermore, as discussed above the value of the selected cutoff was known to be a result-effective variable that affects how the results of the assay are interpreted, i.e. whether a given sample would be classified as positive or negative.

As such, absent evidence of criticality it would have been obvious to one of ordinary skill in the art to divide the net signal ("$Signal_{sample}$" - "$background_{sample}$") taught by U.S. Patent No. 6,815,217 by a cut-off value obtained by multiplying the signal from a negative control by a numerical value. One of ordinary skill in the art would have been motivated to in order to assess the results of the assay and to determine whether a given sample was positive or negative. It would have been further obvious to arrive at the claimed value of *n* (e.g., 2) out of the course of routine optimization, given that the cut-off value (a component of which is n) was recognized in the art as a result-effective variable.

Response to Arguments

29. Applicant's arguments, filed 11/14/2008 have been fully considered.

30. With respect to the rejection of claim 44 under § 112, 2nd paragraph as being indefinite in reciting the term "derived from", Applicant points to the instant amendments to recite that the plurality of analytes are "derived from infection by the pathogen" (Reply, page 8). The Examiner maintains that the scope of the claim is still unclear for reasons set forth above.

31. With respect to the rejections of claims 44-45, 47-48, 73, 76-79, and 81 under 35 § 102(a) as being anticipated by Karl et al., Applicant argues (Reply, pages 11-12) that Karl et al. only teaches detection of one analyte (HBsAg) and therefore fails to specifically teach calculating a

COI for each analyte of a plurality of analytes. Applicant also argues that Karl et al. does not teach simultaneous measuring of a plurality of analytes derived from one pathogen. This is not found persuasive because although the examples of Karl et al. only detected HBsAg, the reference clearly teaches detecting a plurality of analytes. See especially Figure 1 which, as discussed at column 2, lines 62-67, teaches "three different test formats on a single solid phase i.e. to determine HIV antibodies, HBs antigen and anti-HBc antibodies". Thus, the reference clearly teaches detection of a plurality of analytes (HBs antigen and anti-HBc antibodies) derived from one pathogen (Hepatitis B virus). Furthermore, the reference makes clear that each test area is separately analyzed and that a cut-off index is calculated based on each test area (see, e.g., Figure 2 and the examples). The fact that the reference does not provide actual data for a method involving a plurality of analytes from one pathogen is not found persuasive, as it is fairly taught nonetheless.

Applicant further argues that Karl et al. is not enabling (Reply, page 12, first paragraph) but does not elaborate. No evidence or scientific reasoning has been proffered to document why undue experimentation would be required. Such a general allegation is not seen as sufficient evidence to conclude that the reference is non-enabling. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

32. With respect to claims 78-79: In response to applicant's argument (Reply, page 12) that the reference fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., that the parameter $background_{sample}$ refers to "the sample specific background measured for example from the inert solid phase between test spots without

a specific coating") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims do not define the parameter $background_{sample}$ and therefore cannot be construed in the narrow manner argued.

33. With respect to the rejection of claim 46 under § 103 as being unpatentable over Karl et al., Applicant argues that the claim is not obvious because claim 44 is non-obvious (Reply, page 13). However, claim 44 has been rejected as being anticipated by Karl et al. rather than being obvious over the reference.

Applicant also argues as above that Karl et al. does not teach detecting a plurality of analytes or calculating a test area-specific COI for each analyte (Reply, page 13, last paragraph), which arguments have been addressed above.

In response to applicant's argument that Karl et al. does not recognize and appreciate the advantage of a test area-specific COI for each analyte, in that positive detection of a specific analyte is not overshadowed by the high background of other analytes (Reply, paragraph bridging pages 13-14), the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

34. With respect to the rejection of claim 80 under § 103 as being unpatentable over Karl et al. in view of in view of Ohkawa et al., Ohnishi et al., Hyman et al., Chan et al., Lesniewski et al., Kiyosawa et al., and Yuki et al., Applicant's arguments (Reply, pages 14-16) have been fully considered but are not found persuasive.

35. Applicant argues that the Ohkawa et al. and Ohnishi et al. references do not detect a plurality of analytes, and do not use a COI with an adjustable n value. See Reply, page 14. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

36. Applicant also argues that in an ELISA such as taught in Ohkawa, it is not possible to simultaneously measure a sample-specific background (Reply, page 14). This is not found persuasive because the claims do not recite simultaneous measurement. Furthermore, the measurement of background on the same solid phase is taught in the primary reference. In addition, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

37. Applicant argues that none of the secondary references cited teach simultaneously detecting a plurality of analytes (Reply, pages 14-15), which is not persuasive because it amounts to a piecemeal analysis of the references. Further, "simultaneous" measurement is not recited. In the instant case, Karl et al. clearly teach calculation of a COI based on the signal for a single test area, and also makes clear that there may be multiple test areas on a single solid phase to detect multiple analytes in a single sample (i.e., simultaneously).

38. In response to applicant's argument that that none of the secondary references recognizes and appreciates the advantages of a test area-specific COI for each analyte in that positive result of a specific analyte is not overshadowed by the high background of other analytes (Reply, page 15), the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

39. Applicant also argues that the equation disclosed by Karl et al. is fundamentally different from those in the secondary references, in that in Karl et al. the numerator of the equation is adjusted, while in the secondary references the denominator is adjusted (Reply, page 15). Such remarks would only apparently relate to the patentability of claims 78-80, as only these claims define the COI in terms of a specific equation.

As best understood, it appears that Applicant believes that the step of subtracting background in the numerator of the Karl et al. equation would make the resulting equation so unusual that the ordinary artisan would not be motivated to combine it with other art-recognized equations. The Examiner is not persuaded by this line of reasoning. Subtraction of background values is a universal and familiar scientific practice.

In any event, it is maintained for reasons of record that the ordinary artisan, considering the various equations for calculating cut-off values in the prior art references, would appreciate the similarities and would be able to combine the prior art teachings with a reasonable expectation of success. In particular, although Karl et al. did not exemplify varying the denominator (multiplying the negative control signal by the value of "3" in all examples), the

secondary references teach that it was known in the art to vary the denominator in calculating the cut-off index by multiplying the negative control signals by different numbers. For these reasons, the Examiner does not agree that the Karl et al. equation is "fundamentally different" from those in the secondary references.

40. Applicant also argues that the claimed equation is distinct because in Karl et al., the meaning of the parameter $background_{sample}$ is different from the meaning in the instant invention (Reply, paragraph bridging pages 15-16). This is not found persuasive because as discussed above, the claims do not define the parameter $background_{sample}$ and therefore cannot be construed in the narrow manner argued.

41. With respect to the rejections of claims 44-45, 47-48, 73, and 75-77 under §103 as being unpatentable over O'Connor et al., Applicant argues (Reply, pages 16-17) that the reference only theoretically describes the simultaneous determination of an HIV antigen and an HIV antibody, but never shows or enables one of ordinary skill how it is done (Reply, page 16). This is not found persuasive because Applicant has not pointed out why actual data would be necessary or provided evidence or scientific reasoning to support the position that the reference is non-enabling.

42. Applicant further argues that the claimed invention is far more sensitive that that of O'Connor et al. (Reply, page 16). As best understood, Applicant argues for unexpected results.

Whether evidence shows unexpected results is a question of fact and the party asserting unexpected results has the burden of proving that the results are unexpected. In re Geisler, 116 F.3d 1465, 1469-70, 43 USPQ2d 1362, 1364-5 (Fed. Cir. 1997). The evidence must be (1) commensurate in scope with the claimed subject matter, In re Clemens, 622 F.2d 1019, 1035,

206 USPQ 289, 296 (CCPA 1980), (2) show what was expected, to "properly evaluate whether a … property was unexpected", and (3) compare to the closest prior art. Pfizer v. Apotex, 480 F.3d 1348, 1370-71, 82 USPQ2d 1321, 1338 (Fed. Cir. 2007).

In the instant case, no comparative data are provided such that it cannot be properly evaluated whether the purported increase in sensitivity would represent an unexpected result.

43. Applicant further argues that O'Connor does not determine a test area-specific COI because the reference uses a common negative control well (Reply, page 17, first paragraph).

This is not found persuasive because initially, it is noted that the claims require a test area-specific COI but do not clearly require a test area-specific negative control and would therefore not rule out the use of a common negative control. Indeed, the instant claims only recite the use of a single "inert solid phase" for measuring background. Because O'Connor compares the signal from each respective test area (e.g., each well) to the control value, the resulting value would be considered "test area-specific" since it is a function of the signal in the respective test area.

44. Applicant further argues that O'Connor describes measuring extinction in a liquid, which does not permit spatially resolved measurement (Reply, page 17, first paragraph). The Examiner does not agree with this assertion; spatially resolved measurement of a liquid sample is possible when using microtiter plates, which spatially separate different test areas into different wells. This is evident as in the example to which Applicant points (column 9); O'Connor et al. measured the absorbance intensity individually for each well, samples and controls. O'Connor et al. also describe other embodiments other than the microtiter plate-based ELISA of column 9,

indicating that the solid support may be a filter matrix as depicted in the Figure. In any event, the instant claims fail to rule out measuring the signal by absorbance of a liquid.

45. Applicant further argues that O'Connor not teach calculating a "test area-specific COI". This is not found persuasive as the reference teaches dividing the signal from an individual test area (e.g., an individual in the microtiter plate-based ELISA of column 9) by the signal from a negative control sample. Even if each different test spot is compared to the *same* control spot, such a comparison may still be said to be "test area-specific" since it is specific to the signal from the respective test area. Furthermore, the claims recite only a single "inert solid phase" and do not rule out the use of a single region for calculating background for all test areas.

46. Applicant further argues for the superiority of the claimed invention in terms of specificity (Reply, page 17). As discussed above, however, such remarks do not constitute sufficient evidence of unexpected results.

47. With respect to the rejection of claim 46 under § 103 as being unpatentable over O'Connor in view of Ekins, Applicant does not separately argue the limitations of the dependent claim (Reply, page 17, last paragraph).

48. With respect to the rejections of claims 78-80 under § 103 as being unpatentable over O'Connor in view of Carpenter, Ohkawa et al., Ohnishi et al., Hyman et al., Chan et al., Lesniewski et al., Kiyosawa et al., and Yuki et al., Applicant's arguments (Reply, pages 18-19) have been fully considered but are not found persuasive. Applicant argues that none of the cited references teaches or suggests a test area-specific cut-off index for each analyte of a plurality of analytes (Reply, paragraph bridging pages 18-19). This is not found persuasive because as discussed in the rejection, O'Connor clearly teaches assessing the signal from *each respective*

test area in relation to the negative control signal. Such separate analysis is clearly test area-specific.

49. Applicant further argues that Carpenter does not teach simultaneously detecting a plurality of analytes in a sample (Reply, page 19), which is not persuasive because it amounts to a piecemeal analysis of the references. The noted feature is taught in the primary reference.

50. Applicant further argues that Carpenter does not teach or suggest "blanking" the sample signals for each and every analyte, but rather teaches a designated common negative control well (Reply, page 19).

This is not found persuasive because as discussed above, the claims only require that the COI be "test area-specific" and in reciting only a single inert solid phase, do not clearly require the use of multiple inert solid phases for background measurements that correspond to each and every analyte.

Applicant further argues that the $background_{sample}$ of the instant invention is measured for example from the inert solid phase between test spots without a specific coating (Reply, page 19). As discussed above, Applicant has not pointed to any claim language that defines the parameter $background_{sample}$ in the narrow manner argued.

Applicant further argues that spatially resolved measurement in a liquid assay such as ELISA is not possible (Reply, page 19). As discussed above, such purported differences are reflected in the claims. In addition, the Examiner does not agree with this assertion as ELISA permits each spatially separated well to be measured.

51. Applicant further argues that (1) neither O'Connor nor Carpenter teaches or suggests multiplying the negative control signal by an *adjustable value* and that (2) none of the Ohkawa et

al., Ohnishi et al., Hyman et al., Chan et al., Lesniewski et al., Kiyosawa et al., and Yuki et al. references teaches or suggests background subtraction. Applicant's arguments are not persuasive as they focus on the teachings of the individual references and the deficiencies of each, and not what the prior art as a whole would suggest to the ordinary artisan.

52. Applicant further argues that the Examiner has not established why one of ordinary skill in the art would have been motivated to combine different ways of correcting sample signals (Reply, page 19).

Initially, the Examiner notes that an express suggestion is not needed to combine elements of the prior art. "The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965). "There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdiqital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

In the instant case, it is maintained for reasons of record that one would be motivated to combine different known ways to correct sample signals out of the course of routine optimization.

53. With respect to the double patenting rejection over U.S. 6,815,217, it is acknowledged that Applicant has submitted a terminal disclaimer on 11/14/2008. However, the rejection is maintained for reasons of record because the terminal disclaimer was not approved (see above).

Conclusion

54. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Christopher L. Chin/
Primary Examiner, Art Unit 1641